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Supplementary Material

High body mass index and cancer risk

- A Mendelian randomisation study

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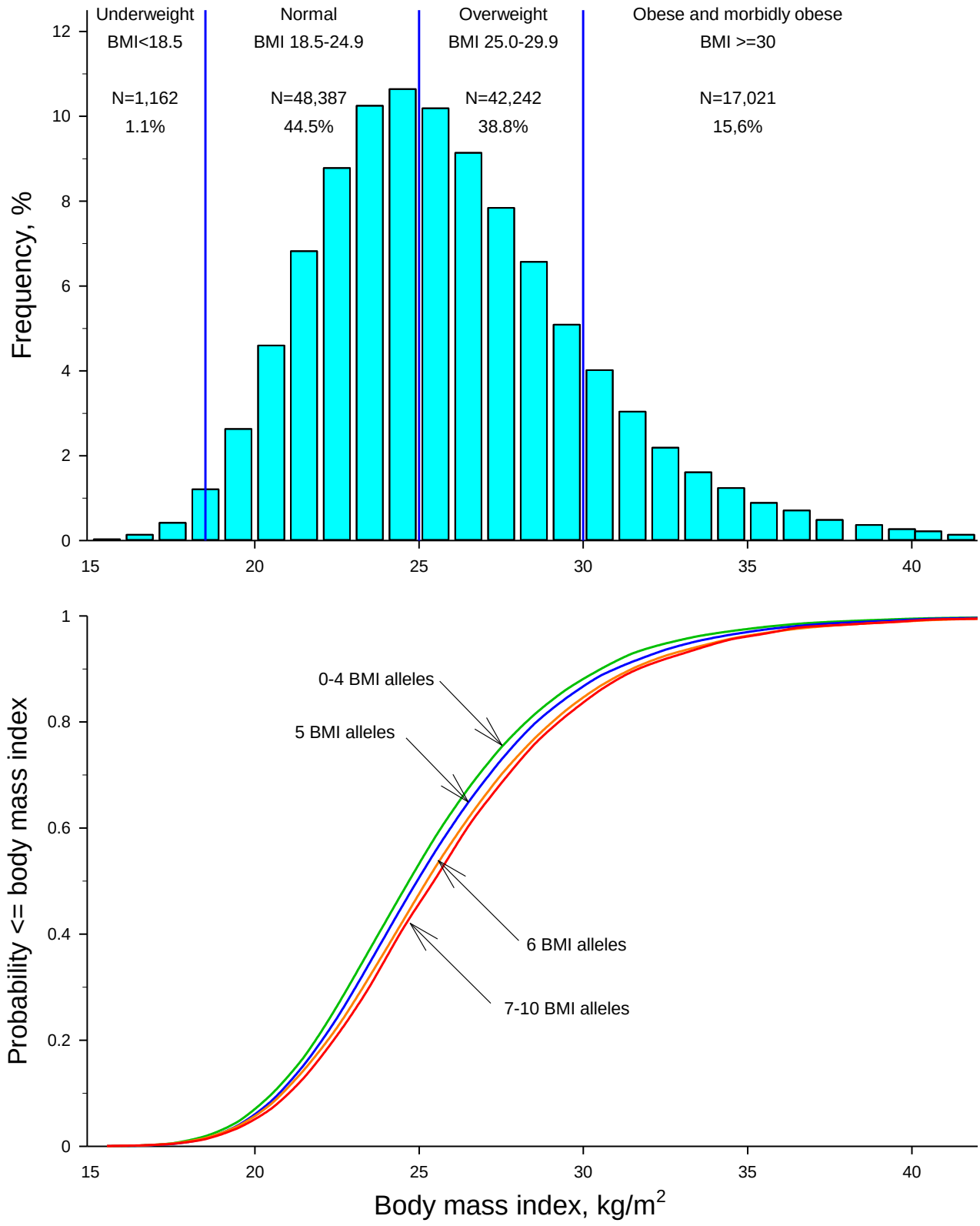
Supplementary Table 1. Baseline characteristics of participants by gender and body mass index category.

	Body mass index, kg/m^2					
	<18.5	**18.5-24.9**	**25-29.9**	**≥30**	**P trend**	**All**
Women						
No. of individuals (%)	976 (1.6%)	31,244 (52.3%)	18,646 (31.2%)	8,906 (14.9%)		59,772 (100%)
Body mass index, kg/m^2	17.9 (17.3-18.3)	22.5 (21.2-23.7)	26.9 (25.9-28.2)	32.7 (31.1-35.4)		24.6 (22.3-27.8)
Age, years	54.0 (42.7-64.0)	53.4 (44.4-63.5)	58.9 (49.0-67.6)	59.2 (49.6-67.3)	<0.001	56.0 (46.3-65.5)
C-reactive protein, mg/L	1.1 (0.7-1.7)	1.3 (0.9-1.8)	1.6 (1.2-2.7)	2.6 (1.6-4.8)	<0.001	1.5 (1.0-2.5)
Current smokers	53%	73%	78%	79%	<0.001	75%
Smoking, pack-years (smokers only)	18 (10-30)	18 (9.6-30)	20 (10-32)	22 (11-35)	<0.001	19 (10-30)
Physical activity						
Low	58%	44%	47%	51%	<0.001	46%
Intermediate	36%	48%	46%	44%	<0.001	47%
High	7%	8%	6%	5%	<0.001	7%
Alcohol consumption, units per week	3 (0-8)	5 (2-10)	5 (2-10)	3 (1-8)	<0.001	5 (2-10)
Education						
Less than 10 years	23%	21%	31%	36%	<0.001	26%
10 to 13 years	45%	55%	51%	46%	<0.001	52%
13 years or more	16%	18%	13%	11%	<0.001	15%
Postmenopausal	62%	57%	70%	72%	<0.001	63%

Men						
No. of individuals (%)	182 (0.4%)	17,143 (35.0%)	23,595 (48.1%)	8,120 (16.6%)		49,040 (100%)
Body mass index, kg/m^2	17.9 (17.4-18.3)	23.4 (22.2-24.2)	27.1 (26.0-28.3)	32.0 (30.8-33.9)		26.2 (24.1-28.7)
Age, years	54.0 (41.3-63.0)	54.0 (44.0-65.0)	57.8 (48.0-67.0)	58.9 (49.4-66.7)	<0.001	56.7 (46.9-66.2)
C-reactive protein, mg/L	1.3 (0.9-2.2)	1.2 (0.8-1.8)	1.5 (1.0-2.3)	2.0 (1.3-3.4)	<0.001	1.4 (1.0-2.3)
Current smokers	36%	66%	74%	76%	<0.001	71%
Smoking, pack-years (smokers only)	30 (20-41)	26 (15-40)	30 (16-44)	31 (18-48)	<0.001	29 (15-43)
Physical activity						
Low	70%	48%	45%	46%	<0.001	46%
Intermediate	23%	42%	44%	43%	<0.001	43%
High	8%	10%	11%	11%	<0.001	10%
Alcohol consumption, units per week	5.5 (0-16)	9 (4-18)	11 (4-20)	10 (3-20)	<0.001	10 (4-19)
Education						
Less than 10 years	19%	22%	29%	38%	<0.001	28%
10 to 13 years	32%	51%	49%	44%	<0.001	49%
13 years or more	20%	17%	15%	11%	<0.001	15%

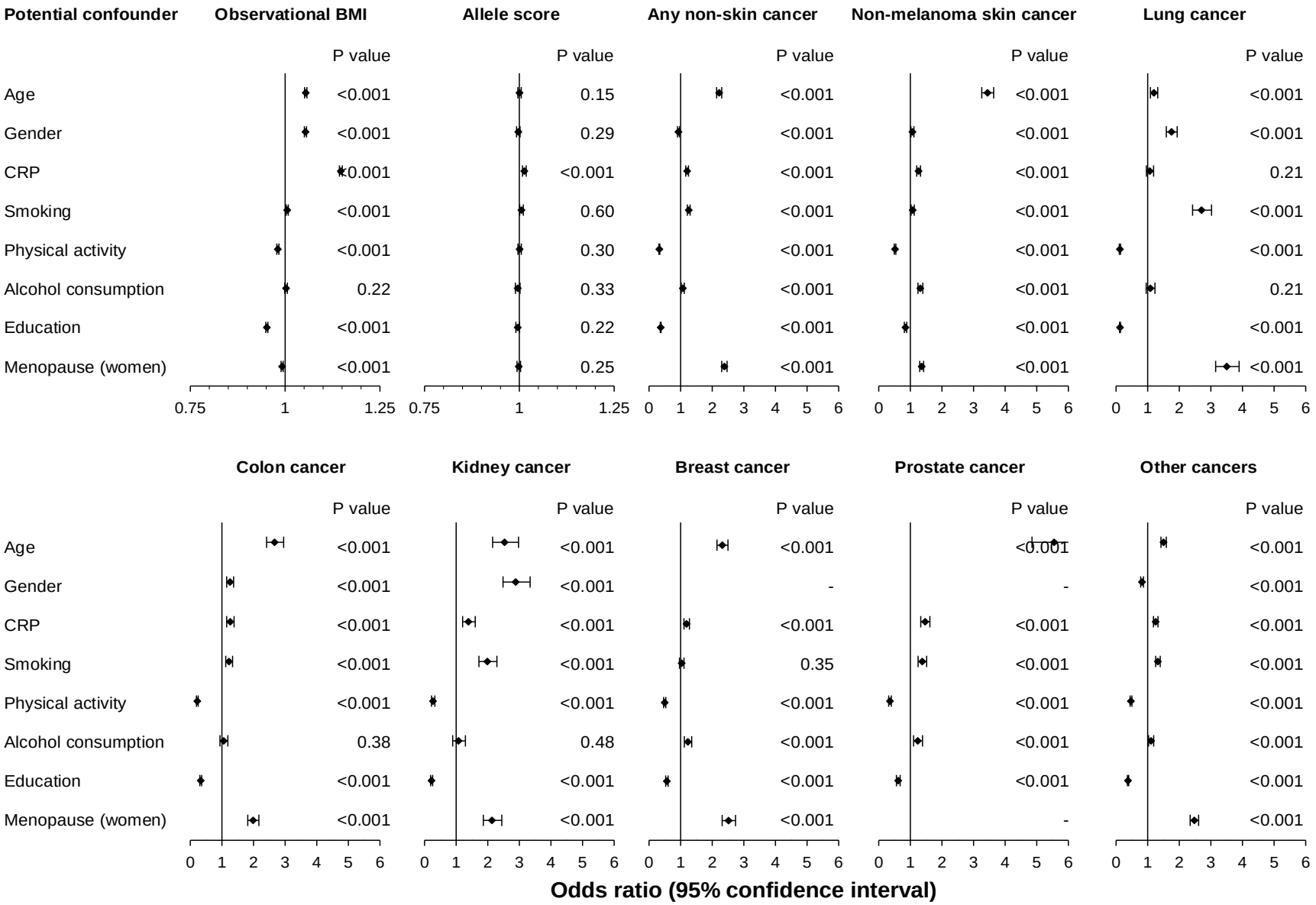
Continuous values are median and interquartile range and categorical values are in percent. 1 unit alcohol=12g.

Supplementary Figure 1.



Distribution of body mass index in the general population (upper panel), the Copenhagen General Population Study and The Copenhagen City Heart Study, and the cumulative distribution function of body mass index (lower panel) showing the probability of a body mass index (y-axis) less than or equal to x as a function of number of body mass index elevating alleles. BMI=body mass index.

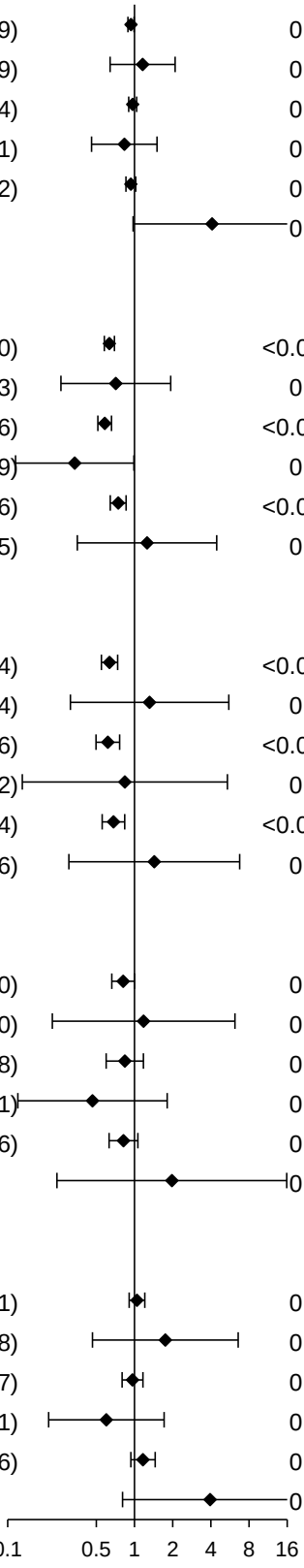
Supplementary Figure 2.



Associations of potential confounders with body mass index, allele score, and cancer. Potential confounders were dichotomized: age (≥55 years versus <55 years), gender (men versus women), C-reactive protein concentrations (≥2mg/L versus <2mg/L), smoking (smoking versus non-smoking), physical activity (intermediate and high versus low), alcohol consumption (>14/21 versus ≤14/21 units per week for women/men), education (≥10 years versus <10 years education), and for women menopausal status (postmenopausal versus premenopausal). For each potential confounder, logistic regression analysis was used to calculate age and gender-adjusted odds ratios and p-values for, respectively, a 1 kg/m^2 increase in observational body mass index, a 1 unit increase in allele score, and for presence versus absence of cancer. BMI=body mass index, CRP=C-reactive protein.

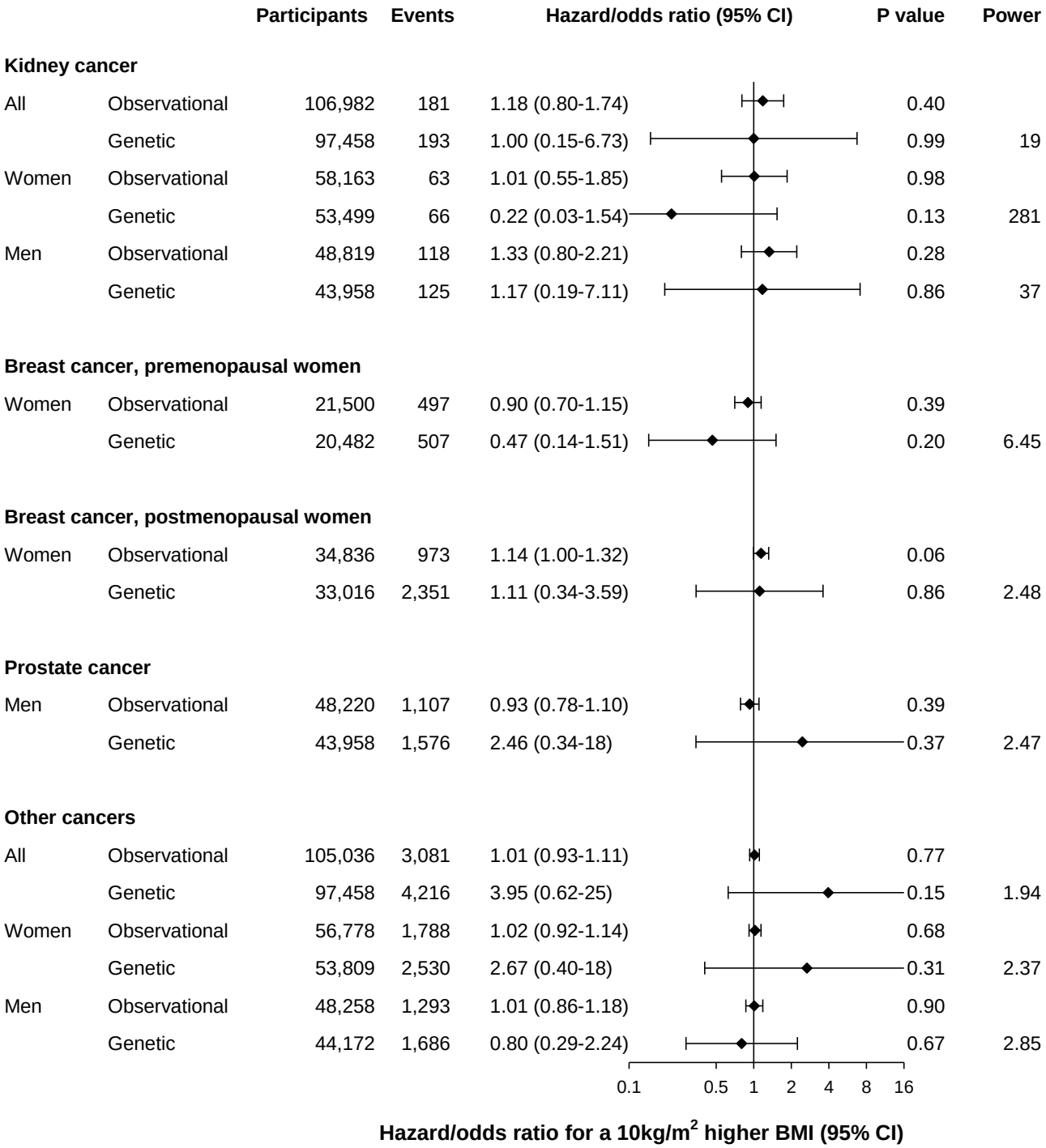
Supplementary Figure 3A.

		Participants	Events	Hazard/odds ratio (95% CI)	P value	Power
Any non-skin cancer						
All	Observational	101.051	8,767	0.94 (0.89-0.99)	0.03	
	Genetic	97,458	11,248	1.16 (0.64-2.09)	0.62	1.54
Women	Observational	54,408	4,472	0.97 (0.90-1.04)	0.37	
	Genetic	53,499	6,376	0.83 (0.46-1.51)	0.55	1.78
Men	Observational	46,643	4,295	0.93 (0.86-1.02)	0.15	
	Genetic	43,958	4,872	4.10 (0.98-17)	0.05	1.93
Non-melanoma skin cancer						
All	Observational	102,809	3,420	0.63 (0.58-0.70)	<0.001	
	Genetic	97,458	7,406	0.71 (0.26-1.93)	0.51	1.68
Women	Observational	55,937	1,800	0.58 (0.52-0.66)	<0.001	
	Genetic	53,499	3,935	0.34 (0.12-0.99)	0.05	2.02
Men	Observational	46,872	1,620	0.74 (0.64-0.86)	<0.001	
	Genetic	43,958	3,470	1.26 (0.35-4.45)	0.72	2.13
Lung cancer						
All	Observational	106,930	1,567	0.64 (0.55-0.74)	<0.001	
	Genetic	97,458	896	1.32 (0.31-5.54)	0.71	4.09
Women	Observational	58,134	646	0.62 (0.50-0.76)	<0.001	
	Genetic	53,499	412	0.84 (0.13-5.42)	0.86	7.46
Men	Observational	48,796	921	0.68 (0.56-0.84)	<0.001	
	Genetic	43,958	484	1.43 (0.30-6.76)	0.65	6.64
Other smoking related cancers (oral, larynx and bladder)						
All	Observational	107,055	720	0.81 (0.66-1.00)	0.05	
	Genetic	97,458	761	1.18 (0.23-6.20)	0.84	4.43
Women	Observational	58,248	222	0.84 (0.60-1.18)	0.31	
	Genetic	53,499	208	0.47 (0.12-1.81)	0.27	17
Men	Observational	48,807	498	0.82 (0.63-1.06)	0.14	
	Genetic	43,958	553	1.97 (0.24-16)	0.52	5.73
Colon cancer						
All	Observational	106,392	1,330	1.05 (0.91-1.21)	0.53	
	Genetic	97,458	1,499	1.75 (0.47-6.58)	0.41	2.98
Women	Observational	57,878	667	0.97 (0.80-1.17)	0.72	
	Genetic	53,499	709	0.60 (0.21-1.71)	0.34	4.87
Men	Observational	48,514	663	1.17 (0.94-1.46)	0.17	
	Genetic	43,958	790	3.95 (0.81-19)	0.09	4.45



Hazard/odds ratio for a 10kg/m^2 higher BMI (95% CI)

Supplementary Figure 3B.

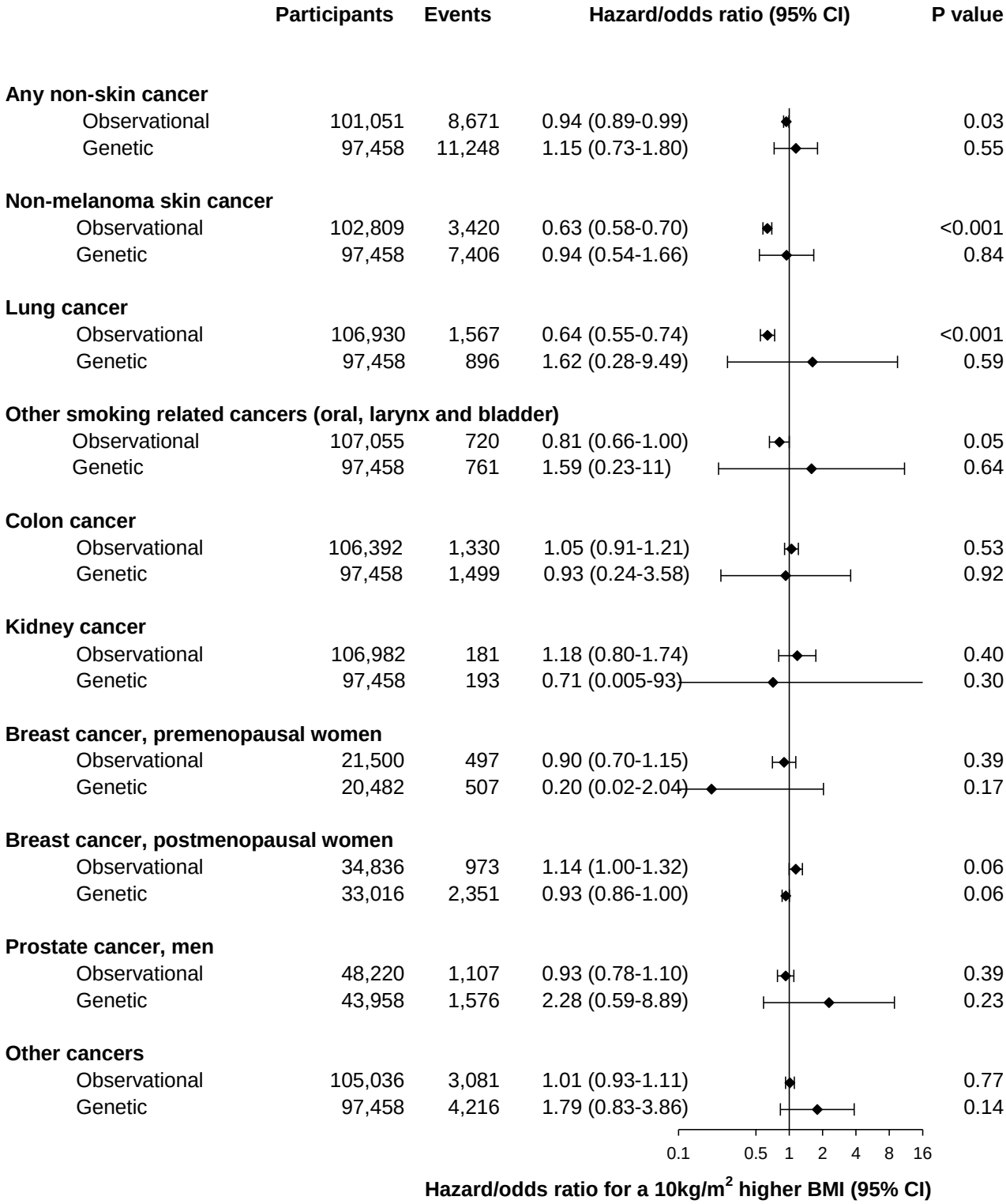


Risk of cancer for a 10kg/m^2 higher, respectively, observational and causal genetically determined body mass index in all participants, and women and men separately. The hazard ratio for a 10 kg/m^2 higher observational body mass index was calculated using Cox regression, while the odds ratio for genetically elevated body mass index was derived from an instrumental variable analysis. P-values

are, respectively, significance of hazard ratios and odds ratios. Power denotes the odds ratio that can be excluded at a two-sided α of 0.05 and ß of 80%.

CI=confidence interval, BMI=body mass index.

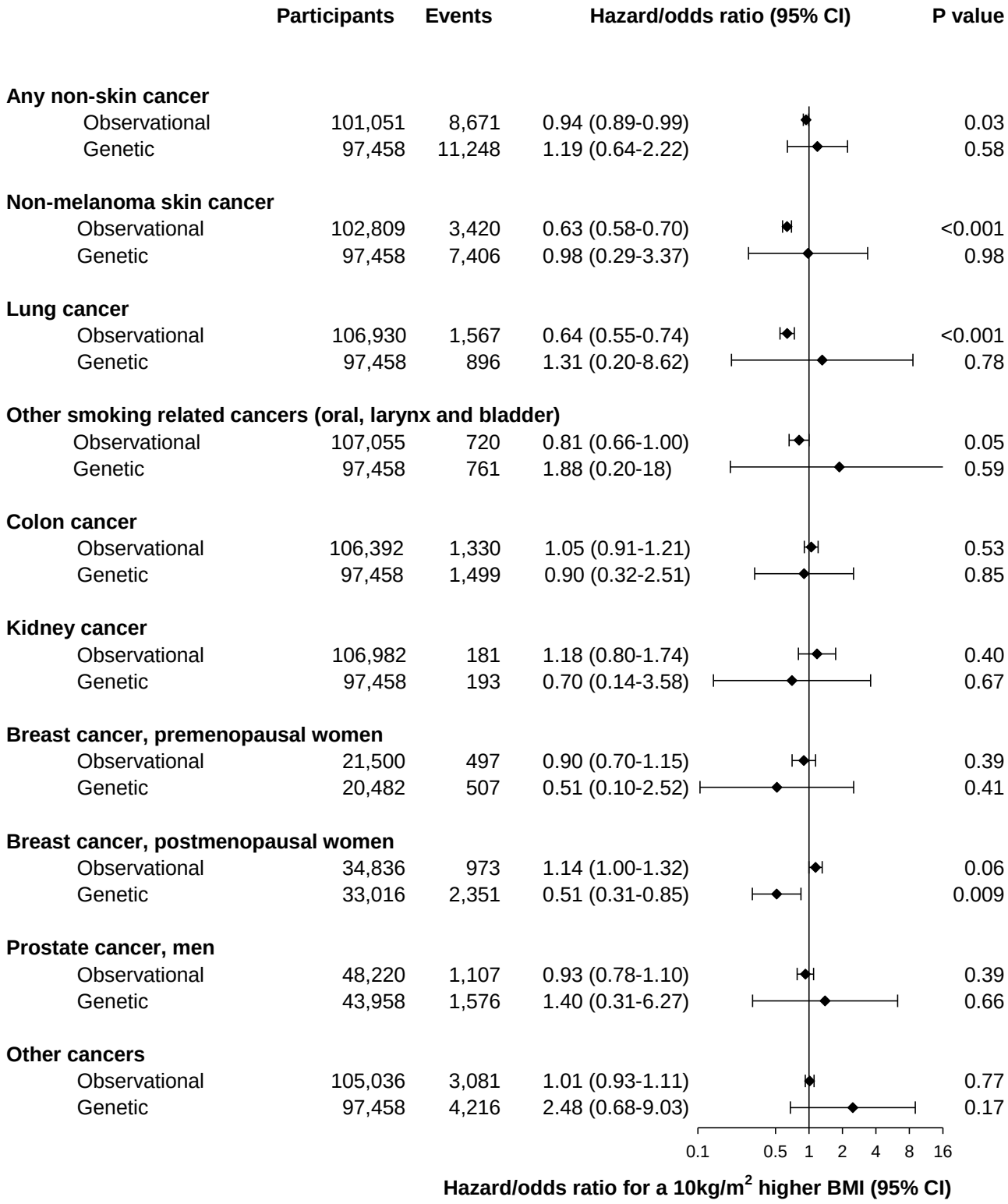
Supplementary Figure 4.



Risk of cancer for a 10kg/m^2 higher, respectively, observational and causal genetically determined body mass index in participants. The odds ratio for genetically elevated body mass index was derived from an instrumental variable analysis using a weighted sum of risk alleles across the five

genotypes applying a weight equal to the effect of each variant on body mass index reported by a previous genome wide association study[1]. The hazard ratio for a 10 kg/m^2 higher observational body mass index was calculated using Cox regression. P-values are, respectively, significance of hazard ratios and odds ratios. CI=confidence interval, BMI=body mass index.

Supplementary Figure 5.



Risk of cancer for a 10kg/m^2 higher, respectively, observational and causal genetically determined body mass index in participants. The odds ratio for genetically elevated body mass index was estimated using an allele score combining the *FTO*(rs9939609), *MC4R*(rs17782313),

TMEM18(rs6548238), and *GNPDA2*(rs10938397) genotypes and thus omitting the *BDNF*(rs10767664) genotype. This was done as a sensitivity analysis, since it has been suggested that this genotype may have a pleiotropic effect on smoking so that the allele associated with a high body mass index is associated with a higher propensity for smoking. The hazard ratio for a 10 kg/m^2 higher observational body mass index was calculated using Cox regression. P-values are, respectively, significance of hazard ratios and odds ratios. CI=confidence interval, BMI=body mass index.

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